HIV-1 P24 antigenaemia does not predict time of survival in AIDS patients

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Abstract

The time of survival in 176 AIDS patients was investigated in relation to the presence or absence of HIV-1 p24 antigenaemia at the moment of diagnosis. The median time of survival in p24 antigen positive patients was 12 months, in p24 antigen negative patients it was 13 months; no difference in survival curves was found. Also no difference was found in survival between patients with high and low p24 antigen levels. The median time of survival in patients for whom a diagnosis of AIDS was made in the period before the introduction of zidovudine treatment was 10 months; in patients diagnosed in the period thereafter it was 18 months ($p < 0.005$). However, when each period was analysed separately, no difference in survival between p24 antigen positive and negative patients was found. Separate analysis of patients with a diagnosis of Kaposi's sarcoma alone showed similar results. HIV-1 p24 antigenaemia at the moment of diagnosis of AIDS (both in the period before and in the period after the introduction of zidovudine) is not a predictor for time of survival.

In asymptomatic subjects infected with the human immunodeficiency virus type I (HIV-1), persistent p24 antigenaemia is associated with an increased risk of rapid disease progression.[1-9]

In this study we tried to resolve the question, whether p24 antigenaemia is a predictor of a more severe course of disease once the diagnosis of AIDS[10,11] had been made. Others came to somewhat conflicting conclusions.[12-14] Steinberg *et al* found no correlation between the presence of p24 antigenaemia and unsuccessful outcome in 58 AIDS patients treated with zidovudine.[12] Dazza *et al* found the clinical course of 56 AIDS patients treated with zidovudine to be independent of the serum level (absent, low or high) of p24 antigen at the start of treatment.[13] Another report, in which no information was given about the use of zidovudine, showed a statistically significant correlation between high serum antigen levels at the time AIDS was diagnosed and short survival.[14] However, the mere presence of detectable p24 antigen was not found to be a prognostic marker.[14]

We investigated retrospectively whether the time of survival of 176 AIDS patients was influenced by the presence or absence of p24 antigenaemia at the moment AIDS was diagnosed. Because a longer time of survival for AIDS patients can be expected in the period after the introduction of zidovudine,[15,16] and because a higher percentage of patients is expected to be p24 antigen negative in the more recent period (given the results of the Amsterdam cohort study of homosexual men),[8] a separate analysis of the periods before and after the introduction of zidovudine treatment in The Netherlands (1 May 1987) was thought to be necessary, to prevent favouring survival time of the group of p24 antigen negative patients.

Patients who presented with Kaposi's sarcoma alone were also analysed separately, given the reported longer median survival time of these patients,[17,18] and the reported relative decrease in incidence of Kaposi's sarcoma.[19]

Patients and methods

PATIENTS

All patients over 18 years old were included, for whom a diagnosis of AIDS was established at the Academical Medical Centre in Amsterdam between 1 January 1986 and 30 April 1987 (group I, n = 92), and between 1 May 1987 and 30 June 1988 (group II, n = 84). Follow up was until 1 September 1989.

Thirty-three patients from group I (36%) received zidovudine after its introduction, 1-14 months after the moment AIDS was diagnosed. For all patients from group II zidovudine treatment was available at the moment AIDS was diagnosed; 70 (83%) from them were actually treated with zidovudine. Patients were classified as having AIDS according to the

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classification of the Centers for Disease Control.[10] After the introduction of its last revised version[11] in one patient from group II the diagnosis of AIDS was made, which would not have been made before this revision (CDC IV-B, HIV-encephalopathy).

Three patients from group II were treated with zidovudine for AIDS related complex (ARC), before they progressed to AIDS (all CDC IV-C1) within this study period. At the start of zidovudine therapy they were p24 antigenaemic, two with serum levels below 200 pg/ml, one with a level above 200 pg/ml. At the moment AIDS was diagnosed (starting-point of this study) they were still p24 antigenaemic, all three with levels below 200 pg/ml.

One hundred and seventy-four patients were men, 166 were homosexuals, three haemophiliacs, two intravenous drug users and three without known risk factors. Two patients were women.

Forty subjects had Kaposi's sarcoma as sole initial diagnosis, 20 in group I and 20 in group II. From group I eight patients (40%) were treated with zidovudine, from group II 16 patients (80%).

LABORATORY EVALUATION

HIV-1 p24 antigen was detected by using a solid-phase, sandwich type immuno-assay (Abbott Laboratories, North Chicago, Il, USA), as previously described.[2] The cut-off value varied from 50–65 pg/ml among samples.

STATISTICAL ANALYSIS

The product-limit estimate by Kaplan and Meier[20] was used to compute cumulative survival curves. Equality of curves was tested by using the log-rank test proposed by Mantel[21] and the generalised Kruskal-Wallis test proposed by Breslow.[22] The first of these tests is more sensitive to late events, whereas the latter gives greater weight to early observations. The statistical analysis was performed using the life Tables and Survival Functions Programs (1L) of the BMDP Statistical Software (1988 release).[23]

Results

At the moment AIDS was diagnosed 97 patients were p24 antigen positive (Ag+) and 79 were p24 antigen negative (Ag−). The median survival time of the Ag+ patients was 12 months, of the Ag− patients 13 months. The difference between the survival curves is statistically not significant, either for late survival ($p = 0{\cdot}30$, Manteltest = M), or for early survival ($p = 0{\cdot}32$, Breslowtest = B) (table).

The median survival time of patients with serum p24 antigen levels <200 pg/ml at the time of diagnosis ($n = 42$) was 11 months, of patients with serum p24 antigen levels $\geqslant 200$ pg/ml ($n = 55$) it was 12 months. This difference is not significant, $p = 0{\cdot}41$ (M) and $p = 0{\cdot}48$ (B).

In group I (diagnosis AIDS before 1 May 1987) 36 out of 92 (39%) patients were Ag−, in group II 43 out of 84 (51%) patients were Ag−. A statistically significant difference was found in survival curves between all (Ag+ and Ag−) patients from group I and all patients from group II: in patients from group I ($n = 92$), median survival was 10 months (see lower 2 lines of Figure), in patients from group II ($n = 84$) it was 18 months (see upper 2 lines of Figure); $p = 0{\cdot}004$ (M) and $p = 0{\cdot}001$ (B).

In group I no difference was found in survival of Ag+ and Ag− patients: median survival was 10 months in Ag+ patients ($n = 56$), median survival was 10 months in Ag− patients ($n = 36$); $p = 0{\cdot}37$ (M) and $p = 0{\cdot}70$ (B) (see Figure and Table). Also in group II no difference in survival of Ag+ and Ag− patients was found: in Ag+ patients ($n = 41$) median survival was 18 months, in Ag− patients ($n = 43$) it was 18 months; $p = 0{\cdot}86$ (M) and $p = 0{\cdot}90$ (B) (see fig and table).

Patients with Kaposi's sarcoma as sole initial diagnosis were analysed separately: 25 were Ag+, 15 Ag−. Median survival of Ag+ patients was 12 months, of Ag− patients it was 13 months; $p = 1{\cdot}00$ (M) and $p = 0{\cdot}63$ (B), the difference was not significant (table). There was a statistically significant difference in survival between patients with Kaposi's sarcoma from group I and II: in patients from group I ($n = 20$) median survival was 11 months, in patients from group II ($n = 20$) it was 24 months; $p = 0{\cdot}02$ (M) and $p = 0{\cdot}02$ (B). In group I median

Table Median time of survival in months in AG+ and AG− patients

	Ag+ (n)	*Ag− (n)*	*P Mantel test*	*P Breslow test*
All AIDS patients	12 (97)	13 (79)	0·30	0·32
Group I	10 (56)	10 (36)	0·37	0·70
Group II	18 (41)	18 (43)	0·86	0·90
Kaposi's sarcoma alone	12 (25)	13 (15)	1·00	0·63
Group I	11 (15)	12 (5)	0·70	0·97
Group II	24 (10)	21 (10)	0·68	0·90
Other diagnoses	11 (72)	13 (64)	0·23	0·36
Group I	10 (41)	10 (31)	0·19	0·40
Group II	16 (31)	16 (33)	0·96	0·83

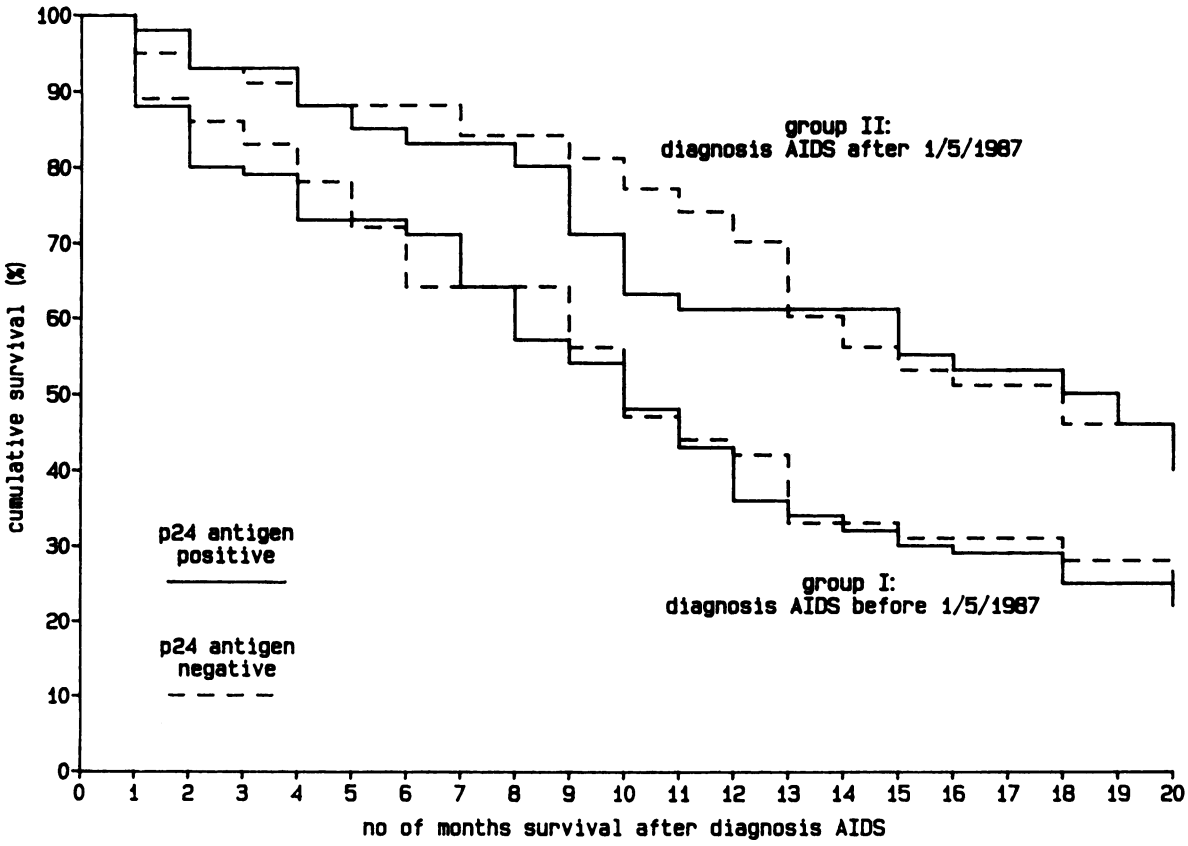

Figure Percentage of patients alive as a function of time after the moment AIDS was diagnosed (calculated by the Kaplan Meier product limit method).

survival of Ag+ patients (n = 15) was 11 months, of Ag− patients (n = 5) it was 12 months. The difference was not significant: p = 0·70 (M) and p = 0·97 (B) (table). In group II median survival of Ag+ patients (n = 10) was 24 months, of Ag− patients (n = 10) 21 months. The difference was not significant: p = 0·68 (M) and p = 0·90 (B) (table).

Separate analysis was also made of patients with presenting diagnosis other than Kaposi's sarcoma alone (n = 136). Median survival of Ag+ patients (n = 72) was 11 months, of Ag− patients (n = 64) it was 13 months; p = 0·23 (M) and p = 0·36 (B), the difference was not significant (table). There was a statistically significant difference in early survival between patients from group I and II without Kaposi's sarcoma: in patients from group I (n = 72) median survival was 10 months, in patients from group II (n = 64) it was 16 months; p = 0·07 (M) and p = 0·01 (B). In group I median survival of Ag+ patients (n = 41) was 10 months, of Ag− patients (n = 31) it was also 10 months. The difference was not significant: p = 0·19 (M) and p = 0·40 (B) (table). In group II median survival of Ag+ patients (n = 31) was 16 months, of Ag− patients (n = 33) it was also 16 months. The difference was not significant; p = 0·96 (M) and p = 0·83 (B) (table).

Discussion

No statistically significant difference was found for time of survival between patients with and without p24 antigenaemia at the moment AIDS was diagnosed. Also, no difference was found in survival between patients with high and low serum p24 antigen levels.

A statistically significant longer time of survival was found in the group of patients with the diagnosis of AIDS after 1 May 1987 compared with the group of patients with that diagnosis before May 1987. This time-related improvement of survival can be ascribed to introduction of zidovudine treatment and to earlier recognition and more effective treatment of opportunistic infections in the more recent period.[15,16] A higher percentage of AIDS patients was found to be negative for p24 antigen in group II compared with group I (51% versus 39%), a trend to be expected from the findings of the Amsterdam cohort study of homosexual men.[8] These results could favour the

time of survival in Ag− patients above Ag+ patients and justify separate analysis of patients in group I and in group II. However, no difference in survival was seen between Ag+ and Ag− patients in group I, nor between Ag+ and Ag− patients in group II.

Separate analysis of patients who presented with diagnosis of Kaposi's sarcoma alone showed a longer time of survival in patients with Kaposi's sarcoma from group II, compared with patients from group I. Presumably this improvement of survival can be ascribed to a delay in the occurrence of opportunistic infections by the use of zidovudine and to more effective treatment of these infections, which are a major cause of death in patients with an initial diagnosis of Kaposi's sarcoma.[24] No difference in survival between Ag+ and Ag− patients with Kaposi's sarcoma was found, either in group I, or in group II. Also for AIDS patients with another presenting diagnosis than Kaposi's sarcoma no difference was found in survival between Ag+ and Ag− patients.

HIV-1 p24 antigenaemia is a predictor of rapid disease progression in asymptomatic HIV-1 infected subjects.[1-9] We conclude that once diagnosis of AIDS has been established p24 antigenaemia has lost its predictive value and its presence or absence is not correlated with time of survival. Our results show that this conclusion is valid in the period before as well as in the period after the introduction of zidovudine treatment.

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